CHAPTER II

Preliminary Classification:
Proposed Class:
Subclass:
NOTE: "All applicants are requested to include a preliminary classification on newly filed patent applications. The preliminary classification, preferably class and subclass designations, should be identified in the upper right-hand corner of the letter of transmittal accompanying the application papers, for example 'Proposed Class 2, subclass 129.' " M.P.E.P. Section 601, 7th ed.

TRANSMITTAL LETTER
TO THE UNITED STATES ELECTED OFFICE (EO/US)
(ENTRY INTO U.S. NATIONAL PHASE UNDER CHAPTER II)

PCT/JP00/04380 — **July 3, 2000,**
INTERNATIONAL APPLICATION NO: INTERNATIONAL FILING DATE

Japanese App. 192993/1999 — **July 7, 1999**
PRIORITY DATE CLAIMED

ARTIFICIAL TUBE FOR NERVE
TITLE OF INVENTION

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APPLICANT(S)

Box PCT - ATTENTION: EO/US
Assistant Commissioner for Patents
Washington D.C. 20231

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service with sufficient postage as **EXPRESS MAIL Label No.: EL931635895US** in an envelope addressed to the: Commissioner for Patents and Trademarks, Washington, D.C. 20231.

Date: January 4, 2002

By: _____
Fatima H. DeArruda

NOTE: To avoid abandonment of the application, the applicant shall furnish to the USPTO, not later than 20 months from the priority date: (1) a copy of the international application, unless it has been previously communicated by the International Bureau or unless it was originally filed in the USPTO; and (2) the basic national fee (see 37 C.F.R. Section 1.492(a)). The 30-month time limit may not be extended. 37 C.F.R. Section 1.495.

WARNING: *Where the items are those which can be submitted to complete the entry of the international application into the national phase are subsequent to 30 months from the priority date the application is still considered to be in the international*

state and if mailing procedures are utilized to obtain a date the express mail procedure of 37 C.F.R. Section1.10 must be used (since international application papers are not covered by an ordinary certificate of mailing - See 37 C.F.R. Section 1.8.

NOTE: Documents and fees must be clearly identified as a submission to enter the national state under 35 USC 371 otherwise the submission will be considered as being made under 35 U.S.C. Section 111. 37 C.F.R. Section 1.494(f).

1. Applicant herewith submits to the United States Elected Office (EO/US) the following items under 35 U.S.C. 371:

a. [X] This express request to immediately begin national examination procedures (35 U.S.C. Section 371(f)).

b. [X] The U.S. National Fee (35 U.S.C. Section 371(c)(1)) and other fees (37 C.F.R. Section 1.492) as indicated below: 2.Fees

CLAIMS FEE	(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) CALCULATIONS
[ ]*	TOTAL CLAIMS	9 - 20 =	0	x $ 18.00 =	$ 0.00
	INDEPENDENT CLAIMS	2 - 3 =	0	x $ 84.00 =	$ 0.00
	MULTIPLE DEPENDENT CLAIM(S) (if applicable) + $280.00				$280.00
BASIC FEE**	[ ] U.S.PTO WAS INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where an International preliminary examination fee as set forth in Section 1.482 has been paid on the international application to the U.S. PTO: [ ] and the international preliminary examination report states that the criteria of novelty, inventive step (non-obviousness) and industrial activity, as defined in PCT Article 33(2) to (4) have been satisfied for all the claims presented in the application entering the national stage (37 C.F.R. Section 1.492(a)(4)) ..... $100.00 [ ] and the above requirements are not met (37 C.F.R. Section 1.492(a)(1)) ..... $710.00 [X] U.S. PTO WAS NOT INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where no international preliminary examination fee as set forth in Section 1.482 has been paid to the U.S. PTO, and payment of an international search fee as set forth in Section 1.445(a)(2) to the U.S. PTO: [ ] has been paid (37 C.F.R. 1.492(a)(2)) ..... $ 740.00 [ ] has not been paid (37 C.F.R. 1.492(a)(3)) ..... $1,040.00 [ ] where a search report on the international application has been [X] prepared by the European Patent Office or the Japanese Patent Office (37 C.F.R. Section 1.492(a)(5)) $890.00				
	Total of above Calculations				= $ 890.00
SMALL ENTITY	Reduction by 1/2 for filing by small entity, if applicable. Affidavit must be filed. (note 37 C.F.R. Sections 1.9, 1.27, 1.28)				- $ 0.00
	Subtotal				$ 1,170.00
	Total National Fee				$ 1,170.00
	Fee for recording the enclosed assignment document $40.00 (37 C.F.R. 1.21(h)). (See Item 13 below). See attached "ASSIGNMENT COVER SHEET".				$ 40.00
TOTAL	Total Fees enclosed				$ 1,210.00

* See attached Preliminary Amendment Reducing the Number of Claims.

i. [X] A check in the amount of **$ 1,210.00** to cover the above fees is enclosed.

ii. [ ] Please charge Account No. in the amount of $.

A duplicate copy of this sheet is enclosed.

*** WARNING: "To avoid abandonment of the application the applicant shall furnish to the United States Patent and Trademark Office not later than the expiration of 30 months from the priority date: * * * (2) the basic national fee (see Section 1.492(a)). The 30-month time limit may not be extended." 37 C.F.R. Section 1.495(b).*

WARNING: If the translation of the international application and/or the oath or declaration have not been submitted by the applicant within thirty (30) months from the priority date, such requirements may be met within a time period set by the Office. 37 C.F.R. Section 1.495(b)(2). The payment of the surcharge set forth in Section 1.492(e) is required as a condition for accepting the oath or declaration later than thirty (30) months after the priority date. The payment of the processing fee set forth in Section 1.492(f) is required for acceptance of an English translation later than thirty (30) months after the priority date. Failure to comply with these requirements will result in abandonment of the application. The provisions of Section 1.136 apply to the period which is set. Notice of Jan. 3, 1993, 1147 O.G. 29 to 40.

3. [X] A copy of the International application as filed (35 U.S.C. Section 371(c)(2)):

NOTE: Section 1.495 (b) was amended to require that the basic national fee and a copy of the international application must be filed with the Office by 30 months from the priority date to avoid abandonment "The International Bureau normally provides the copy of the international application to the Office in accordance with PCT Article 20. At the same time, the International Bureau notifies applicant of the communication to the Office. In accordance with PCT Rule 47.1, that notice shall be accepted by all designated offices as conclusive evidence that the communication has duly taken place. Thus, if the applicant desires to enter the national stage, the applicant normally need only check to be sure the notice from the International Bureau has been received and then pay the basic national fee by 30 months from the priority date." Notice of Jan. 7, 1993, 1147 O.G. 29 to 40, at 35-36. See item 14c below.

a. [ ] is transmitted herewith.
b. [ ] is not required, as the application was filed with the United States Receiving Office.
c. [X] has been transmitted
   i. [X] by the International Bureau.
   Date of mailing of the application (from form PCT/IB/308): 02 November 2000
   ii. [ ] by applicant on .
   Date

4. [X] A translation of the International application into the English language (35 U.S.C. Section 371(c)(2)):
a. [X] is transmitted herewith.
b. [ ] is not required as the application was filed in English.
c. [ ] was previously transmitted by applicant on Date
d. [ ] will follow.

5. [ ] Amendments to the claims of the International application under PCT Article 19 (35 U.S.C. Section 371(c)(3)):

NOTE: The Notice of January 7, 1993 points out that 37 C.F.R. Section 1.495(a) was amended to clarify the existing and continuing practice that PCT Article 19 amendments must be submitted by 30 months from the priority date and this deadline may not be extended. The Notice further advises that: "The failure to do so will not result in loss of the subject matter of the PCT Article 19 amendments. Applicant may submit that subject matter in a preliminary amendment filed under Section 1.121. In many cases, filing an amendment under Section 1.121 is preferable since grammatical or idiomatic errors may be corrected." 1147 O.G. 29-40, at 36.

a. [ ] are transmitted herewith.
b. [ ] have been transmitted
   i. [ ] by the International Bureau.

Date of mailing of the amendment (from form PCT/IB/308): .

ii. [ ] by applicant on .

c. [X] have not been transmitted as

i. [X] applicant chose not to make amendments under PCT Article 19.
Date of mailing of Search Report (from form PCT/ISA/210): .

ii. [ ] the time limit for the submission of amendments has not yet expired. The amendments or a statement that amendments have not been made will be transmitted before the expiration of the time limit under PCT Rule 46.1.

6. [ ] A translation of the amendments to the claims under PCT Article 19 (38 U.S.C. Section 371(c)(3)):
   a. [ ] is transmitted herewith.
   b. [ ] is not required as the amendments were made in the English language.
   c. [ ] has not been transmitted for reasons indicated at point 5(c) above.

7. [X] A copy of the international examination report (PC T/IPEA/409)
   [X] is transmitted herewith.
   [ ] is not required as the application was filed with the United States Receiving Office.

8. [ ] Annex(es) to the international preliminary examination report
   a. [ ] is/are transmitted herewith.
   b. [ ] is/are not required as the application was filed with the United States Receiving Office.

9. [ ] A translation of the annexes to the international preliminary examination report
   a. [ ] is transmitted herewith.
   b. [ ] is not required as the annexes are in the English language.

10. [X] An oath or declaration of the inventor (35 U.S.C. Section 371(c)(4)) complying with 35 U.S.C. 115
   a. [ ] was previously submitted by applicant on . Date
   b. [X] is submitted herewith, and such oath or declaration
      i. [X] is attached to the application.
      ii. [X] identifies the application and any amendments under PCT Article 19 that were transmitted as stated in points 3(b) or 3(c) and 5(b); and states that they were reviewed by the inventor as required by 37 C.F.R. Section 1.70.
   c. [ ] will follow.

Other document(s) or information included:

11. [X] An International Search Report (PCT/ISA/210) or Declaration under PCT Article 17(2)(a):
   a. [X] is transmitted herewith.
   b. [X] has been transmitted by the International Bureau.
      Date of mailing (from form PCT/IB/308): 02 November 2000 .
   c. [ ] is not required, as the application was searched by the United States International Searching Authority.
   d. [ ] will be transmitted promptly upon request.

e. [ ] has been submitted by applicant on Date

12. [X] An Information Disclosure Statement under 37 C.F.R. Sections 1.97 and 1.98:
a. [X] is transmitted herewith.
Also transmitted herewith is/are:
[X] Form PTO-1449 (PTO/SB/08A and 08B).
[X] Copies of citations listed. (7)
b. [ ] will be transmitted within THREE MONTHS of the date of submission of requirements under 35 U.S.C. Sections 371(c).
c. [ ] was previously submitted by applicant on Date

13. [X] An assignment document is transmitted herewith for recording.

A separate [X] "COVER SHEET FOR ASSIGNMENT (DOCUMENT) ACCOMPANYING NEW PATENT APPLICATION" or[ ] FORM PTO 1595 is also attached.

14. [X] Additional documents:
a. [X] Copy of request (PCT/RO/101)

b. [X] International Publication No. WO 01/03609
i. [ ] Specification, claims and drawing
ii. [X] Front page only

c. [ ] Preliminary amendment (37 C.F.R. Section 1.121)

d. [X] Other

1. Published PCT, Application No. **PCT/JP00/04380**

2. PCT Request in Japanese – PCT/RO/101

3. Form PCT/IB/301 – Notification of Receipt of Record Copy

4. Form PCT/IPEA/402 - Notification of Receipt of Demand

5. Form PCT/IB/304 – Notification Concerning Submission or Transmittal of Priority Document

6. Form PCT/IB/308 - Notice Informing The Applicant of The Communication of The International Application To the Designated Offices

7. Form PCT/IB/332 - Information Concerning Elected Offices Notified of Their Election

8. Form PCT/IB/338 – Notification of Transmittal of Copies of Translation of The International Preliminary Examination Report

15. [X] The above checked items are being transmitted
    a. [X] before 30 months from any claimed priority date.
    b. [ ] after 30 months.

16. [ ] Certain requirements under 35 U.S.C. 371 were previously submitted by the applicant on , namely:

AUTHORIZATION TO CHARGE ADDITIONAL FEES

WARNING: *Accurately count claims, especially multiple dependent claims, to avoid unexpected high charges if extra claims are authorized.*

NOTE: "A written request may be submitted in an application that is an authorization to treat any concurrent or future reply, requiring a petition for an extension of time under this paragraph for its timely submission, as incorporating a petition for extension of time for the appropriate length of time. An authorization to charge all required fees, fees under Section 1.17, or all required extension of time fees will be treated as a constructive petition for an extension of time in any concurrent or future reply requiring a petition for an extension of time under this paragraph for its timely submission. Submission of the fee set forth in Section 1.17(a) will also be treated as a constructive petition for an extension of time in any concurrent reply requiring a petition for an extension of time under this paragraph for its timely submission." 37 C.F.R. Section 1.136(a)(3).

NOTE: "Amounts of twenty-five dollars or less will not be returned unless specifically requested within a reasonable time, nor will the payer be notified of such amounts; amounts over twenty-five dollars may be returned by check or, if requested, by credit to a deposit account." 37 C.F.R. Section 1.26(a).

[X] The Commissioner is hereby authorized to charge the following additional fees that may be required by this paper and during the entire pendency of this application to Account No. 04-1105.

[X] 37 C.F.R. Section 1.492(a)(1), (2), (3), and (4) (filing fees)

WARNING: *Because failure to pay the national fee within 30 months without extension (37 C.F.R. Section 1.495(b)(2)) results in abandonment of the application, it would be best to always check the above box.*

[X] 37 C.F.R. Section 1.492(b), (c) and (d) (presentation of extra claims)

NOTE: Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must only be paid or these claims cancelled by amendment prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 C.F.R. Section 1.492(d)), it might be best not to authorize the PTO to charge additional claim fees, except possible when dealing with amendments after final action.

[X] 37 C.F.R. Section 1.17 (application processing fees)
[X] 37 C.F.R. Section 1.17(a)(1)-(5)(extension fees pursuant to Section 1.136(a).
[ ] 37 C.F.R. Section 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 C.F.R. Section 1.311(b))

NOTE: Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the notice of allowance. 37 C.F.R. Section 1.311(b).

NOTE: 37 C.F.R. 1.28(b) requires "Notification of any change in loss of entitlement to small entity status must be filed in the application . . . prior to paying, or at the time of paying . . . issue fee." From the wording of 37 C.F.R. Section 1.28(b): (a) notification of change of status must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity.

[ ] 37 C.F.R. Section 1.492(e) and (f) (surcharge fees for filing the declaration and/or filing an English translation of an International Application later than 30 months after the priority date).

Respectfully submitted,

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Date: January 4, 2002

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BOS2_186857.1

4/pts

DESCRIPTION

ARTIFICIAL TUBE FOR NERVE

Technical Field

The present invention relates to an artificial tube for nerve.

Background Art

In the case of peripheral nerve being severed surgically or severed due to injury, an initial attempt is made to directly anastomose the stumps of the severed peripheral nerve. In many cases, however, it is impossible to accurately anastomose the severed nerve directly resulting in the nerve being left in the severed state. Consequently, although the nerve attempts to regenerate towards the distal side, it is impaired by connective tissue. Hence, regeneration stops with the formation of a neuroma at the severed end without reaching the neural stump on the distal side. As a result, the function of the severed nerve is frequently not restored after the surgical wound or injury has healed, and sequella remain. In cases in which direct anastomosis is not possible, a peripheral nerve having a function which is not very important may be partially excised from the same patient, and autotransplantation may be performed to the severed site of the nerve using this peripheral nerve segment. However, in this method as well, not only are there many cases in which nerve function is not adequately restored, but there are also many cases in which decreased function is observed even at the portion at which the transplanted nerve is used.

Therefore, numerous attempts have been made to restore function by connecting the stumps of severed peripheral

nerves with a tube-shaped material, namely an artificial tube for nerve, regenerating the axon from the stump on the central side of the nerve trunk towards the stump on the distal side, inducing the nerve to extend in the proper direction, and allowing the nerve to reach a myoneural junction or peripheral sensory receptor from the peripheral nerve trunk. In the past, various materials have been attempted to be used as artificial tube for nerve, examples of which include non-porous tubes made of silicone, polyethylene or polyvinyl chloride, porous tubes made of drawn polytetrafluoroethylene or cellulose, semi-permeable membrane tubes made of polyacrylonitrile or polysulfone, tubes made of biodegradable materials such as polyglycolic acid, polylactic acid or their copolymers, gelatin tubes, or biological tissue tubes originating in the same species such as arteries and veins. However, in regeneration experiments on peripheral nerves using these materials, since biological repair is impaired by the material, the length of nerve that has been able to be regenerated thus far has been at most on the order of 15 mm. In addition, not only is the regenerated nerve narrow without the form of the nerve being normally restored, but there are also many cases in which the function of regenerated nerve is not restored. In addition, although examples have been reported in which neural growth factor NGF is filled into a tube, since NGF ends up rapidly running out of the tube and dispersing, remarkable effects have not been obtained.

Although artificial tubes for nerve which comprise collagen tubes in which collagen fibers on which laminin and fibronectin are coated are filled (Tong, X., et al., Brain Research 663: 155-162 (1994), have recently been attempted, since the collagen tubes are unable to remain without being broken down until the nerve is regenerated to an adequate length, satisfactory results have not been obtained.

On the other hand, the spinal cord is considered to not

regenerate once it has been damaged. In the case the spinal cord is damaged due to injury or tumor, the damaged spinal cord does not regenerate, and all function below the damaged portion is lost with paralysis remaining as the sequella. Recently however, experiments on animals have begun to be conducted that prove that the spinal cord is also able to regenerate. In the case the spinal cord is severed sharply and accurately re-sutured, function is restored and the damaged portion is repaired to a considerable degree. In addition, if a portion of the spinal cord is excised in the form of a tube and an intercostal nerve fasicle is implanted at that site, the portion of the spinal cord regenerates and function is at least partially restored. If a portion of the spinal cord is excised in the form of a tube, and fetal spinal cord is transplanted to that site, spinal cord function and form are restored. These findings have been observed in experiments in rats. In this case as well, it is recognized that regeneration occurs only in the case the transplanted fetal spinal cord segment is transplanted by properly aligning the respective neural processes. Based on the above findings, although it has been determined that regeneration of the spinal cord can occur by inducing the spinal cord so as to properly align the compartments of regenerated tissue, there have been no artificial tubes for spinal cord developed whatsoever that actually allow spinal cord regeneration.

Therefore, in order to control the rate of decomposition in the body so as to remain in the body until the nerve regenerates while also allowing degradation and absorption in the body as nerve regeneration progresses, the development of an artificial tube for nerve is desired that induces axons regenerated from severed nerve stumps to extend in the proper direction without pressing on the regenerated nerve following nerve regeneration, and causes rapid restoration of blood flow by promoting infiltration

of blood capillaries from the body to promote regeneration of nerve tissue. In addition, there is also an urgent need for the development of an artificial tube for spinal cord that connects not only peripheral nerves but also the missing portions of spinal cord, and promotes proper regeneration of spinal cord tissue along with restoration of function.

Disclosure of the Invention

The present invention relates to an artificial tube for nerve which is characterized in that the artificial tube for nerve has fine fibrous collagen bodies (30) in the lumen of a tube (10, 20) comprised of a biodegradable and absorbable material, the voids inside the fine fibrous collagen bodies being filled with laminin.

In addition, the present invention relates to a method for producing an artificial tube for nerve which is characterized in that the method comprises steps: preparing a tube (10, 20) comprised of a biodegradable and absorbable material, introducing a hydrochloric acid solution of collagen into the lumen of the tube, freezing and then freeze-drying the tube to form fine fibrous collagen bodies (30), performing thermal crosslinking treatment on the tube having the fine fibrous collagen bodies in its lumen, and introducing laminin into the fine fibrous collagen bodies.

Brief Description of the Drawings

Fig. 1 is a drawing showing a cross-section of an embodiment of an artificial tube for nerve of the present invention (that provides a schematic representation of the structure without using actual dimensions. In addition, although the portion indicated by reference numeral 30 is an actual object, the diagonal lines are omitted for the sake of the explanation.)

Fig. 2 is a photograph (SEM photograph) showing the structure (cross-section) of an artificial tube for nerve of type 1 of the present invention.

Fig. 3 is a photograph (SEM photograph) showing the structure (cross-section) of tube base material of an artificial tube for nerve of type 2 of the present invention.

Fig. 4 is a photograph (SEM photograph) showing the structure (cross-section) of the fine fibrous collagen bodies present in the tube lumen of the artificial tube for nerve of the present invention.

The following reference numerals are used in the drawing.

11,21: (Biodegradable, absorbable material) tube
12,13: (Gelatin) coating layer
22,23: (Collagen) coating layer
30: Fine fibrous collagen bodies

Best Mode for Carrying Out the Invention

Although the length and inner diameter of the tube (10, 20) that composes the artificial tube for nerve of the present invention differ according to the length and thickness of the severed portion of the nerve, in order to cover, for example, a missing portion on the order of about 25 mm of the sciatic nerve (using the example of a cat), the length is about 28-35 mm, and preferably about 30 mm, and the inner diameter is about 1-8 mm, and preferably about 4 mm. In addition, in the case of using the artificial tube for nerve of the present invention as an artificial tube for spinal cord as well, the length of the tube is determined according to the length of the severed portion, while the inner diameter is preferably about 2-12 mm and particularly preferably about 10 mm.

It is necessary that the tube (10, 20) composed of a material that is biodegradable and absorbable in vivo that

composes the artificial tube for nerve of the present invention retains the shape of the tube to prevent invasion of body cells from outside the tube during the time until the severed nerve regenerates and the severed location is rejoined (about 1-3 months). Consequently, despite being biodegradable and absorbable in vivo, it is necessary that the material is able to retain its shape in the body for a certain period of time. Although examples of base materials of such a material include mesh materials selected from the group consisting of polyglycolic acid, polylactic acid, copolymer of glycolic acid and lactic acid, copolymer of lactic acid and ε-caprolactone, polydioxanone and copolymer of glycolic acid and trimethylene carbonate, a mesh tube comprised of polyglycolic acid is preferable. In addition, in addition to the above-mentioned mesh tube, a tube comprised of fine fibrous collagen can also be used preferably.

To begin with, a description is provided of the artificial tube for nerve of the present invention (hereinafter referred to as "Type 1") in which a tube comprised of a biodegradable and absorbable material has a coating layer (13, 23) comprised of gelatin or collagen on at least the outside of a mesh tube comprised of a material such as polyglycolic acid. In order to allow the mesh tube (11) comprised of a material such as polyglycolic acid to retain the shape of the tube for a period of about one to three months in the body, the thickness of the tube (referring to the thickness of the tube wall in the form of a cylinder, and to apply similarly hereinafter) is preferably about 0.1-3 mm, and particularly preferably about 0.5-2 mm. If the thickness exceeds about 3 mm, the tube obstructs regeneration of body tissue, and if the thickness is less than 0.1 mm, degradation and absorption of the tube proceed too rapidly, and the shape of the tube is not maintained until the nerve finishes regenerating. In addition, in the case of using the artificial tube for

nerve of the present invention as an artificial tube for spinal cord, its thickness should preferably be about 0.2-5 mm, and particularly preferably about 0.5-3 mm.

In the case that the base material of the above tube is a material such as polyglycolic acid, said tube is in the form of a mesh to impart water permeability to the base material which is itself hydrophobic. The mesh pore size of this mesh tube (11) is preferably about 5-30 μm, and particularly preferably about 10-20 μm. If the mesh pore size is less than about 5 μm, cells and tissue are unable to proliferate, while if the mesh pore size exceeds about 30 μm, entry of tissue becomes excessive.

In addition, since said material itself does not have an action that promotes tissue regeneration, although it is made to have a coating layer (13, 23) comprised of a material having action that promotes tissue regeneration on at least the outside of tube (11) serving as the base material, it is preferably coated or filled with a material having action that promotes tissue regeneration on both the inside and outside of the tube serving as said base material and inside the mesh pores. The thickness of the coating layers (13,23 and/or 12,22) is preferably about 0.2-5 mm, and particularly preferably 0.5-3 mm. Examples of such materials that promote tissue regeneration include collagen or gelatin which have water-permeability, do not cause foreign body reactions when applied in the body, have excellent bioaffinity and tissue compatibility, and have an action that promotes tissue regeneration. Collagen originating in various animals conventionally used in the past can be used for the collagen raw material, preferable examples of which include type I collagen or a mixture of type I and type III collagen originating in the skin, bone, cartilage, tendon and organs of cows, pigs, rabbits, sheep, kangaroos or birds that is solubilized by acid, base, enzymes and so forth. The coating layers composed of collagen are layers having an amorphous structure in which

collagen molecules are dispersed. Purified gelatin according to the Japanese Pharmacopoeia can be used for the raw material of a coating layer composed of gelatin.

In the artificial tube for nerve of the present invention, the tube base material composed of a material that is biodegradable and absorbable in vivo can be the mesh tube (11) composed of a material such as the above-mentioned polyglycolic acid, or a tube (21) composed of fine fibrous collagen having collagen having an action of promoting tissue regeneration for its raw material. The following provides a description of the artificial tube for nerve of the present invention (hereinafter referred to as "Type 2") in which the material that is biodegradable and absorbable in vivo is a tube composed of fine fibrous collagen, and the coating layer (23 and/or 22) possessed on at least the outside of said tube is composed of collagen.

Type I collagen or a mixed collagen of type I and type III of animal origin like that has been used in the past and is solubilized by acid, base or enzymes and so forth in the same manner as the raw material of the coating layer of the artificial tube for nerve of type 1 is preferable for the collagen used for the raw material of said tube base material. This material composed of fine fibrous collagen is a matrix or thread-like woven or knitted product of a non-woven fabric-like multi-element structure in which fine fibers composed of collagen molecules are overlapped in multiple layers (and more specifically, using microfibers having a diameter of 3-7 nm composed of several collagen molecules as the basic unit, said microfibers are bundled to form ultrafine fibers having a diameter of 30-70 nm, said ultrafine fibers are further bundled to form fine fibers having a diameter of 1-3 μm, rows of bundles of said fine fibers are laminated vertically and horizontally in alternating fashion to form fibers having a diameter of 5-8 μm, and said fibers are fallen on top of one another in a coaxial direction to form sheet fibers having a diameter of

20-50 μm, ultimately resulting in the formation a fibrous collagen as the maximum unit by randomly intermingling these sheet fibers 11; see Fig. 2). Tube (21) that uses this for its material has an inner diameter and length similar to tube (11) of the artificial tube for nerve of type 1. Its thickness is preferably about 0.5-5 mm, and particularly preferably 1-2 mm. In addition, in the case of using the artificial tube for nerve of the present invention as an artificial tube for spinal cord, its thickness is preferably about 0.5-5 mm, and particularly preferably about 1-3 mm. In addition, the coating layer (23 and/or 22) composed of collagen formed on at least the outside of this tube (21) uses conventional solubilized type I or a mixed collagen of type I and type III of animal origin for its raw material similar to the non-woven fabric-like multi-element structure composed of fine fibrous collagen for the tube base material. However, the form is that of a layer having an amorphous structure in which collagen molecules are dispersed. Furthermore, the thickness of the coating layer is preferably about 0.1-2 mm, and particularly preferably about 0.5-1 mm.

As previously described in details, the artificial tube for nerve of the present invention has fine fibrous collagen bodies (30) in the lumen of a tube (10,20) composed of a biodegradable and absorbable material, and laminin is filled in the voids in said fine fibrous collagen bodies (here, said fine fibrous collagen bodies have a structure that is substantially similar to the non-woven fabric-like multi-element structure composed of fine fibrous collagen serving as the tube base material; see Fig. 3). When this artificial tube for nerve is applied in the body, nerve fibers use said fine fibrous collagen bodies as footholds for regeneration for the purpose of regenerating and extending. (Furthermore, said fine fibrous collagen bodies are gradually digested and destroyed during the course of regeneration and extension

of nerve fibers.)

As a preferable mode of the present invention, the tube base material (11 or 21) composed of a material that is biodegradable and absorbable in vivo is a tube (11) composed of a cylindrical mesh body made of polyglycolic acid, and the coating layer (23 and/or 22) of said tube is composed of amorphous collagen.

The following provides a description of the method for producing the artificial tube for nerve of the present invention. To begin with, in order to produce the artificial tube for nerve of type 1, a mesh tube (11) is first produced using a material such as polyglycolic acid. Although this may be produced by any method, as an example of such a method, fibers of polyglycolic acid and so forth (fibers having a diameter of, for example, 0.1 mm) are woven into the shape of a cylinder to obtain a mesh tube having the above thickness. The prepared mesh tube (11) is then coated with the above collagen or gelatin solution or immersed in said solution (this coating or immersion is to be hereinafter referred to as "Coating") and then air-dried to form a collagen or gelatin coating layer (13,23 and/or 12,22) on at least the outside of mesh tube (11) and inside the mesh pores (in the case of forming said collagen or gelatin coating layer only on the outside of said mesh tube and inside the mesh pores, a rod made of Teflon and so forth that makes contact with the inside of said mesh tube should be inserted into the lumen of said mesh tube prior to coating of said collagen or gelatin solution). In order to form this collagen or gelatin coating layer, an approximately 1 N hydrochloric acid solution (pH of about 3) preferably containing about 1-3 wt%, and particularly preferably about 1-2 wt%, of collagen, or preferably an about 2-30 wt%, and particularly preferably about 10-20 wt%, aqueous gelatin solution is used. Furthermore, in this type of artificial tube for nerve, it is convenient to coat mesh tube (11) with collagen or gelatin after treating

with plasma discharge, ozone emission or other hydrophilization treatment to impart mesh tube (11) with hydrophilic properties.

On the other hand, in order to prepare the artificial tube for nerve of type 2, a rod made of Teflon and so forth that makes contact with the inside of the tube and has, for example, a diameter of about 1-8 mm, and preferably about 4 mm, is used for the core. Furthermore, in the case of using the artificial tube for nerve of the present invention as an artificial tube for spinal cord, the rod having a diameter of preferably about 2-12 mm, and particularly preferably about 10 mm, is used. The core is immersed in an approximately 1 N hydrochloric acid solution containing preferably about 0.5-3 wt%, and particularly preferably about 1-2 wt%, of collagen, and a collagen hydrochloric acid solution layer having a thickness of preferably about 5-20 mm, and particularly preferably about 10 mm, is formed on the surface of said core followed by freezing (for example, at about 0°C for about 12 hours). Furthermore, in the case of using the artificial tube for nerve of the present invention as an artificial tube for spinal cord, a collagen hydrochloric acid solution layer is formed having a thickness of preferably about 5-30 mm, and particularly preferably about 20 mm, followed by freezing. As a result of freezing, fine fragments of ice form between the collagen molecules dispersed in the hydrochloric acid solution, phase separation occurs in the collagen hydrochloric acid solution, and fine fibers of collagen are formed due to rearrangement of the collagen molecules. Next, this is further freeze-dried (for example, at about 0°C for about 24 hours) in a vacuum. As a result of freeze-drying, in addition to the fine ice fragments between the collagen molecules vaporizing, a tube is obtained composed of a non-woven fabric-like collagen layer in which fine fibers of collagen overlap in multiple layers.

Next, the core on which is formed this fine fibrous collagen layer is placed in a pouch made of polyethylene and so forth, sealed and degassed or not degassed followed by mechanical pressing of said fine fibrous collagen layer to compress the collagen layer. As a result of compressing, high-density, fine fibrous collagen layer (21) is obtained. This compression procedure is performed such that the thickness of said fine fibrous collagen layer after compression is preferably about 0.5-5 mm, and particularly preferably about 1-2 mm, or in the case of using as an artificial tube for spinal cord, the compression procedure is performed such that the thickness of the fine fibrous collagen layer after compression is preferably about 0.5-5 mm, and particularly preferably about 1-3 mm. Furthermore, in the case of using that in which a collagen thread-like product is woven or knitted for the tube composed of fine fibrous collagen, in place of forming the above collagen hydrochloric acid solution layer, wet spinning is performed to first produce a collagen thread-like product from the above collagen hydrochloric acid solution after which this is woven or knitted into the shape of a tube. The remainder of the procedure starting with freezing is the same as that described above.

Collagen coating layer (23 and/or 22) is further formed on at least the outside of compressed fine fibrous collagen layer (21) formed in this manner. As a result of forming these collagen coating layers (23 and/or 22), a tube (20) composed of a biodegradable and absorbable material is obtained having even greater strength. In order to form these collagen coating layers (23 and/or 22), the tube composed of fine fibrous collagen layer (21) removed from the above-mentioned rod or core is preferably again coated with or immersed in an approximately 1 N hydrochloric acid solution containing preferably about 0.5-3 wt%, and particularly preferably about 1-2 wt%, collagen, and a

collagen hydrochloric acid solution layer is formed on at least the outside of fine fibrous collagen layer (21) followed by air-drying. This coating or immersion and air-drying procedure is repeated several times, and preferably 5-20 times, to obtain a collagen coating layer (23 and/or 22) having an amorphous structure in which collagen molecules are dispersed (the thickness of the collagen hydrochloric acid solution layer is preferably about 0.2-1.0 mm, and particularly preferably about 0.5 mm, overall). In the case of using the artificial tube for nerve of the present invention as an artificial tube for spinal cord, the thickness is the same.

Tube (20) prepared in this manner can be handled easily and allows easy suturing with nerves due to its high tear strength as compared with a tube consisting of compressed fine fibrous collagen layer (21) alone (due to partial entry of amorphous collagen into said compressed fine fibrous collagen layer and partial dissolution and precipitation of collagen at the interface of said compressed fine fibrous collagen layer and said collagen coating layer).

Fine fibrous collagen bodies (30) are formed in the lumen of tube (10,20) composed of a biodegradable and absorbable material prepared as described above. Formation of these fine fibrous collagen bodies (30) should be performed in the same manner as formation of the tube (21) of type 2 with the exception of not performing the core filling and compression procedure. In other words, the above collagen hydrochloric acid solution is poured into the lumen of these tubes using tube (10) or tube (20) as a kind of mold followed by freezing and freeze-drying.

Furthermore, prior to formation of these fine fibrous collagen bodies (30), crosslinking treatment is performed in order to impart resistance to water-solubility to tube (21) composed of the collagen or gelatin coating layer (13,23 and/or 12,22) and compressed fine fibrous collagen

(in the case of type 2, this crosslinking treatment may also be performed after preparing tube (21) and before formation of the coating layer (23 and/or 22). Crosslinking treatment is advantageous for the artificial tube for nerve of the present invention because it maintains the shape of the tube and prevents invasion of cells from outside the artificial tube for nerve during the time until the peripheral nerve is finished regenerating.

Although varying according to the length of the severed nerve portion that requires regeneration (since the imparting of the shape retention function of the tube serves as the rate-determining step in the body), crosslinking treatment is performed to an extent that the shape of the tube is retained for 1-3 months after application in the body. Although examples of crosslinking methods include gamma ray crosslinking, ultraviolet ray crosslinking, electron beam crosslinking, thermal dehydration crosslinking, glutaraldehyde crosslinking, epoxy crosslinking and water-soluble carbodiimide crosslinking, thermal dehydration crosslinking is preferable because it is easy to control the degree of crosslinking and does not have an effect on the body even when used for crosslinking treatment. The crosslinking treatment is performed in a vacuum at a temperature of, for example, about 105-150°C, preferably about 120-150°C, and particularly preferably about 140°C, for, for example, about 6-24 hours, preferably about 6-12 hours, and particularly preferably about 12 hours.

Finally, a component that aids the growth of nerve fibers is filled into the voids in the above fine fibrous collagen bodies (30). Preferable examples of such a component include laminin, and particularly preferably human laminin. As an example of a filling method, tube (10,20) having fine fibrous collagen bodies (30) in its lumen is immersed in a solution of laminin dissolved in PBS (Phosphate Buffered Saline), or a PBS solution of laminin

is injected into said fine fibrous collagen bodies. However, prior to this laminin filling step, crosslinking treatment, and preferably thermal dehydration crosslinking treatment, is preferably performed on the said fine fibrous collagen bodies produced for the same reasons as in the production step of fine fibrous collagen bodies (30). Furthermore, in the case of using the artificial tube for nerve of the present invention as an artificial tube for spinal cord, an additional component for promoting regeneration and extension of nerve fibers, such as at least one among cell nutrient/growth factors like TGF-β, inflammatory cells including autologous macrophages (cultured in vitro) and autologous, homologous or heterologous myelin (medullary sheath) forming cells such as oligodendroglia and Schwann cells, are preferably introduced into said fine fibrous collagen bodies in addition to this laminin filling. Introduction of these additional components should be carried out in accordance with routine methods. After filling and introducing these components that aid in nerve regeneration and extension, the entire structure is air-dried to complete production of the artificial tube for nerve of the present invention (naturally, this does not mean that procedures required for distribution on the market, such as packaging and sterilization, do not have to be carried out).

The artificial tube for nerve prepared in the manner described above can be used to restore nerve function by inserting both stumps of a nerve that has been severed by injury or surgical procedure into the present artificial tube for nerve and fixing those portions by knotting suture to induce axon regeneration and extension in the proper direction, and allow axons to reach from the peripheral nerve trunk to a neuromuscular junction or peripheral sensory receptor. In addition, in the case the spinal cord is damaged due to injury as well, by removing the vertebrae corresponding to the damaged portion and covering the

damaged portion of the spinal cord with the present artificial tube for nerve, it is believed that the damaged spinal cord can be regenerated and its function restored.

Although the following provides a detailed explanation of the present invention through its examples and comparative examples, the present invention is not limited to these.

Example

Polyglycolic acid (PGA) fibers (diameter: 0.1 mm) were woven into a tubular shape to prepare a polyglycolic acid mesh tube (mesh pore size: approximately 10-20 μm) having a length of about 100 mm, inner diameter of about 4-5 mm and thickness of about 1 mm. By making its surface hydrophilic by subjecting to plasma discharge treatment and immersing this mesh tube in 1 N hydrochloric acid solution containing 1.0 wt% enzyme-solubilized collagen originating in pig skin and then air-drying, the inside and outside of the tube were coated with said collagen hydrochloric acid solution (and naturally the insides of the mesh pores were also filled with said collagen hydrochloric acid solution; here, the immersion and drying procedure was repeated 10 times).

Next, after performing thermal dehydration crosslinking treatment (140°C x 24 hr) on the above tube having collagen coating layers on its inside and outside, the above collagen hydrochloric acid solution was poured into its lumen followed by freezing (-20°C x 24 hr), freeze-drying (-80°C x 48 hr under vacuum) and performing thermal dehydration crosslinking treatment (140°C x 24 hr) again.

The above tube having fine fibrous collagen bodies in its lumen following crosslinking treatment obtained in this manner was immersed in a PBS solution of human laminin (concentration: 10 μg/ml) followed by air-drying (this procedure was repeated three times) to obtain the artificial tube for nerve of the present invention (Type 1).

80 mm of the common peroneal nerve of dogs (body

weight: 10 kg) was excised, the nerve stumps on both ends were inserted into the above-mentioned artificial tube for nerve and the overlapping portions of said artificial tube for nerve and said nerve stumps were fixed by knotting suture with 10-0 Nylon thread followed by evaluation over time.

Comparative Example

Enzyme-solubilized collagen fibers originating in pig skin (diameter: about 5 μm) subjected in advance to thermal dehydration crosslinking treatment (140°C x 24 hr) were immersed in a PBS solution of human laminin (concentration: 10 μg/ml) followed by air-drying (this procedure was repeated three times) to obtain about 80 laminin-coated collagen fibers that were inserted into the lumen of the above PGA mesh tube having collagen coating layers on its inside and outside so that the fibers were substantially parallel to the axis of said tube, and observations similar to the example were conducted using the resulting artificial tube for nerve.

Observation Results

In the case of the comparative example, abnormal stance of the affected rear paw when stationary and claudication when walking were observed at one month after surgery, and delay of the above stance and walking abnormality were observed in the majority of the animals even at three months after surgery. In contrast, in the example, similar functional abnormalities were observed to be diminished at one month after surgery, and both had nearly completely disappeared at three months after surgery. According to the results of electrophysiological tests, the amount of time from disappearance of response immediately after surgery to re-induction became shorter for both the somatosensory electric potential (SEP), which expresses recovery of sensory nerves, and the compound muscle activation potential (CMAP), which expresses recovery of motor nerves, and the recovery index was also promoted at

three months after surgery.

Industrial Applicability

The artificial tube for nerve of the present invention is able to retain its shape until the nerve finishes regenerating. In addition, since it induces and promotes nerve regeneration, severed nerves regenerate faster and longer in comparison with conventional artificial tubes for nerve, the state of the regenerated nerve more closely approaches the normal state, and recovery of nerve function is also favorable. In addition, it can also be used as an artificial tube for spinal cord for regeneration and recovery of damaged spinal cord.

CLAIMS

1. An artificial tube for nerve having fine fibrous collagen bodies in the lumen of a tube comprised of a biodegradable and absorbable material, the voids inside the fine fibrous collagen bodies being filled with laminin.

2. The artificial tube for nerve according to claim 1, wherein the biodegradable and absorbable material is a mesh material composed of a material selected from the group consisting of polyglycolic acid, polylactic acid, copolymer of glycolic acid and lactic acid, copolymer of lactic acid and ε-caprolactone, polydioxanone and copolymer of glycolic acid and trimethylene carbonate, and has a coating layer composed of gelatin or collagen on at least the outside of said tube.

3. The artificial tube for nerve according to claim 2, wherein the mesh material has a mesh pore size of about 5-30 μm.

4. The artificial tube for nerve according to claim 1, wherein the biodegradable and absorbable material is composed of fine fibrous collagen, and has a coating layer composed of collagen at least on the outside of said tube.

5. The artificial tube for nerve according to any of claims 1 to 4, wherein at least one of cell nutrient/growth factors, autologous inflammatory cells or autologous, homologous or heterologous myelin forming cells are additionally introduced into the fine fibrous collagen bodies.

6. A method for producing an artificial tube for nerve comprising steps: preparing a tube comprised of a biodegradable and absorbable material, introducing a

hydrochloric acid solution of collagen into the lumen of the tube, freezing and then freeze-drying the tube to form fine fibrous collagen bodies, performing thermal crosslinking treatment on the tube having the fine fibrous collagen bodies in its lumen, and introducing laminin into the fine fibrous collagen bodies.

7. The method according to claim 6, wherein the tube comprised of a biodegradable and absorbable material is obtained by coating a gelatin or collagen solution onto at least the outside of a mesh material composed of a material selected from the group consisting of polyglycolic acid, polylactic acid, copolymer of glycolic acid and lactic acid, copolymer of lactic acid and ε-caprolactone, polydioxanone and copolymer of glycolic acid and trimethylene carbonate, air-drying and subjecting to thermal crosslinking treatment.

8. The method according to claim 6, wherein the tube comprised of a biodegradable and absorbable material is obtained by coating a hydrochloric acid solution of collagen onto the surface of a core material, freezing and then freeze-drying to obtain a layer composed of fine fibrous collagen, compressing the fine fibrous collagen layer, coating a gelatin or collagen solution onto at least the outside of the compressed fine fibrous collagen layer, air-drying and subjecting to thermal crosslinking treatment.

9. The method according to either of claims 7 or 8, wherein at least one kind of cell nutrient/growth factors, separately cultured autologous inflammatory cells or autologous, homologous or heterologous myelin forming cells loaded onto gelatin or collagen are introduced into the fine fibrous collagen bodies into which laminin has been introduced.

Fig. 1

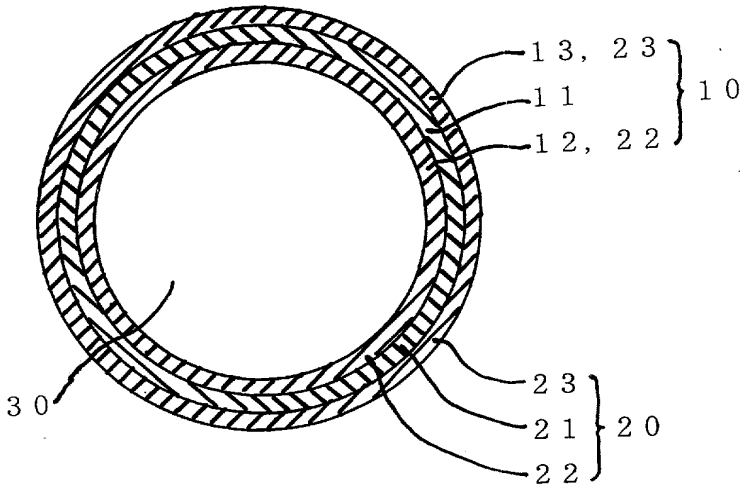


Fig. 2

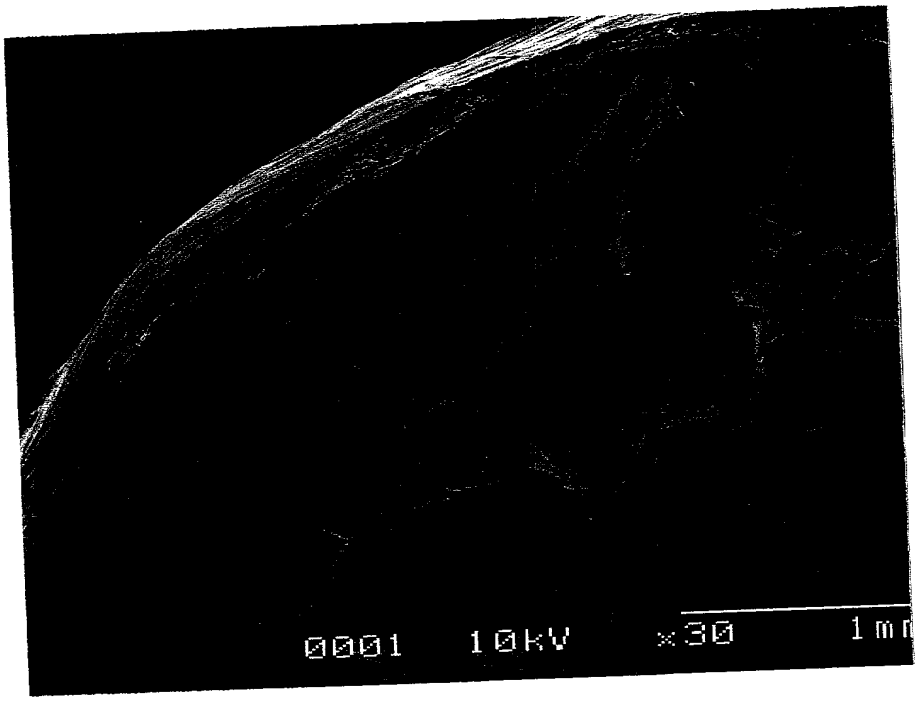


Fig. 3

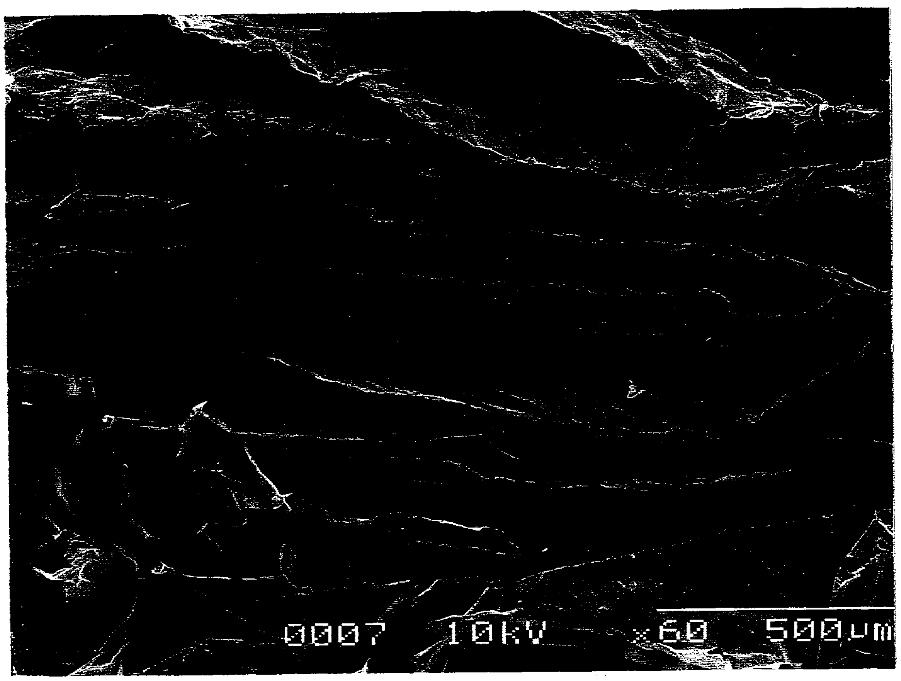
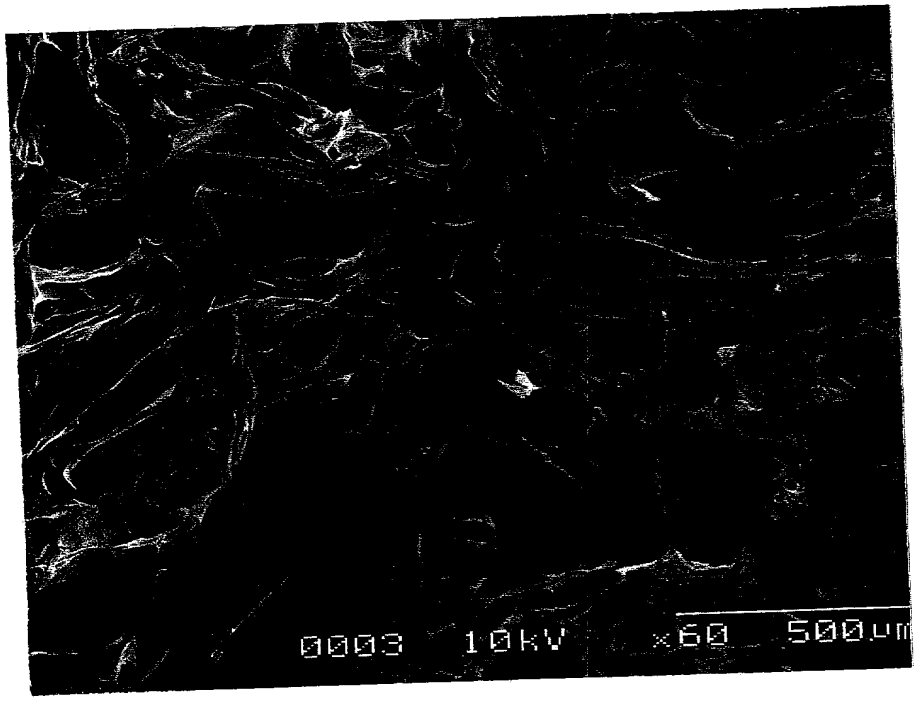


Fig. 4



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DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that: My residence, post office address and citizenship are as stated below next to my name. I believe I am the original, first and sole inventor (if only one name is listed at 201) below or an original, first and joint inventor (if plural names are listed at 201-208 below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

ARTIFICIAL TUBE FOR NERVE

which is described and claimed in:

☐ the specification attached hereto.

☐ the specification in U.S. Application Serial Number _____, filed on _____.

☒ the specification in PCT international application Number PCT/JP00/04380 filed on 03.07.2000; and was amended on _____.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a). I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

Prior Foreign/PCT Applications and Any Priority Claims Under 35 U.S.C. 119:			
Application No.	Filing Date	Country	Priority Claimed Under 35 U.S.C. 119?
192993/1999	07/July/1999	Japan	☒YES ☐NO
			☐YES ☐NO
			☐YES ☐NO
			☐YES ☐NO
			☐YES ☐NO
			☐YES ☐NO
			☐YES ☐NO

I hereby claim the benefit under 35 U.S.C. §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below, and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose material information as defined in 37 CFR §1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

Prior U.S. Applications or PCT International Applications Designating the U.S-Benefit Under 35 U.S.C. §120					
U.S. Applications			Status (Check One)		
Application Serial No.		U.S. Filing Date	Patented	Pending	Abandoned
PCT Applications Designating the U.S.					
Application No.	Filing Date	U.S. Serial No. Assigned			

SCANNED, # 12

CLAIM FOR BENEFIT OF PRIOR U.S. PROVISIONAL APPLICATION(S)
(35 U.S.C. § 119(e))

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

Applicant	Provisional Application Number	Filing Date

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) with full powers of association, substitution and revocation to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

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I hereby further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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